Physical Exercise: A Versatile Anti-Inflammatory Tool Involved in the Control of Hypothalamic Satiety Signaling

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ABSTRACT

The hypothalamus plays a critical role in the control of food consumption and energy expenditure. Fatty diets can elicit an inflammatory response in specific hypothalamic cells, including astrocytes, tanycytes, and microglia, disrupting anorexigenic signals in region-specific hypothalamic neurons, contributing to overeating and body weight gain. In this study, we present an update regarding the knowledge of the effects of physical exercise on inflammatory signaling and circuits to control hunger in the hypothalamus in obesity conditions. To try to understand changes in the hypothalamus, we review the use of magnetic resonance/anorexigenic hormone analysis in humans, as well as in animal models to explore the physiological and molecular mechanism by which exercise modulates satiety signals, such as the central anti-inflammatory response, myokine delivery from skeletal muscle, and others. The accumulation of scientific evidence in recent years allows us to understand that exercise contributes to weight control, and it is managed by mechanisms that go far beyond "burning calories."

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INTRODUCTION

The hypothalamus is recognized as the master regulator of energy homeostasis, directly controlling food intake and energy expenditure. Dysfunctions in hypothalamic neuronal regions or subpopulations are strongly associated with increased or reduced body weight. In the last decades, the hypothalamic inflammatory process has been linked to the signaling loss of anorexigenic hormones, leptin, and insulin (13, 19, 30, 88). Consequently, the functional disturbance of insulin and leptin in the hypothalamus favors a positive energy balance, culminating in body fat tissue enhancement. Body fat weight gain has been primarily associated with several comorbidities, and in this sense, obesity could be considered the century's juggernaut disease. Pharmacological treatments and invasive interventions such as bariatric surgery have been effective in weight loss; however, weight loss is not sustained with these alone. Thus, non-invasive, less costly, and side effects free interventions are needed to fight against this disease (21, 44, 79, 98).

Several researchers have sought to understand how nutritional and physical activity strategies can modulate energy homeostasis, with a direct impact on weight loss, mainly on preventing weight regain. The vital work published by King and coworkers was able to demonstrate that the appetite stimulus was transiently inhibited during and after high-intensity exercise in healthy lean men (62). Therefore, the term "exercise-induced anorexia" was adopted and opened up new exploratory avenues concerning the suppressive effects of exercise over appetite in humans (11, 12, 61). Furthermore, research using animal and human models has been performed to understand the molecular and hormonal mechanisms by which physical exercise can contribute to the control of food intake (11, 12, 61, 78, 108, 138). The knowledge that substances secreted by skeletal muscle (myokines) during and after contractile activity could reach and alter central nervous system (CNS) functioning changed the status quo of the predictable actions of exercise, transposing the benefits of physical exercise to another level of conceptualization. Some of these myokines orchestrate concatenated intracellular signaling, decreasing the proinflammatory molecules, and improving circulating

factors with suppressive effects on appetite, such as leptin and insulin. The understanding of endoplasmic reticulum stress over-response control and anti-apoptotic effects induced by these myokines, which protect the brain areas from neuronal damage caused by obesity, has projected sport sciences into this new field of investigation, called "immunometabolism and exercise" (78, 124, 138, 169).

Although it seems evident that regular physical exercise contributes to the reduction of body weight, it is essential to clarify that this can happen not only because energy expenditure is increased, but also because food intake is reduced. In addition to the peripheral effects, physical exercise promotes similar actions in the CNS, which are decisive for the control of body weight. Therefore, the pathophysiological basis for the illustrious description of the Roman poet Juvenal *"mens sana in corpore sano"* has been elaborated (75). Despite the scarcity of molecular mechanistic explanations involving the control of food intake in humans, in 2010, Ropelle *et al.*, using exercise protocols in rodents, proposed a new interpretation of cytokine actions in the CNS, which could protect against hypothalamic dysfunction induced by obesity. In this elegant study, acute exercise improved insulin and leptin sensitivity in specific neuronal subpopulations in the hypothalamus, causing anorexia in obese rodents (124).

Thus, in the present review, we will discuss the acute and chronic effects of physical exercise on the control of food intake in rodents and humans. Moreover, we will address the primary physiological and molecular mechanisms involved in physical exercise-induced appetite suppression, especially in the context of obesity.

CENTRAL CONTROL OF FOOD INTAKE

The control of food intake and thermogenesis are dynamic and complex processes, which makes understanding the hypothalamic function vitally important. Specific hypothalamic neuronal populations play a central role in integrating peripheral signals, such as leptin, insulin, and nutrients, apprising whole-body energy status, and activating particular signaling routes to induce or suppress the appetite and thermogenesis (97). After sensing these signals, specific neuronal subpopulations are also activated by synaptic transducers to perform a particular action, in a coordinated manner, across accurate controls.

Firstly, the hypothalamic arcuate nucleus (ARH) is composed of at least two specialized populations of first-order neurons that recognize mainly insulin and leptin and synthesize diffuse neuropeptides (through orexigenic or anorexigenic actions). These neurons have a spatial ability, giving the subjects the first notions of their hunger state. These neurons produce neuropeptide Y (NPY) and the agouti-related protein (AgRP), with orexigenic actions. In the vicinity of the AgRP/NPY neurons, other neuronal populations synthesize and secrete anorexigenic neurotransmitters such as proopiomelanocortin (POMC), releasing the melanocyte-stimulating hormone (α-MSH), and the cocaine and amphetamine-regulated transcript (CART) (60, 97). Therefore, the POMC/CART specialized neurons have an anorexigenic/thermogenic effect, while the NPY/AgRP specialized neurons are orexigenic/anti-thermogenic.

Secondly, axonal connections are established between first-order ARH neurons (POMC/CART and NPY/AgRP) and second-order neurons located in other hypothalamic nuclei such as the paraventricular nucleus (PVN), ventromedial nucleus (VMN), dorsomedial nucleus (DMN), and lateral area of the hypothalamus (HL). These areas are involved in a definitive and robust act of seeking food or food aversion, and in starting or stopping energy expenditure by the organism (60, 167). Neuronal projections from POMC/CART in ARH to PVN neurons induce the activation and release of the thyrotropin-releasing hormone (TSH) and corticotrophin-releasing hormone (CRH), both responsible for a strong anorexic stimulus (food aversion) and energy expenditure through thermogenesis. On the other hand, neuronal projections from NPY/AgRP in ARH to the HL induce orexin and melanin-concentrating hormone (MCH) production, both of which also have substantial orexigenic and anti-thermogenic repercussions (33, 145). Finally, thermogenesis is directly controlled in the brown adipose tissue. To increase or decrease its functioning, efferent neuronal projections connect HL and PVN neurons to brown adipose tissue, blocking or releasing catecholamines directly to β3-receptors in brown adipocytes (95, 96).

Disorders in neuronal functioning/connections in these different hypothalamic nuclei circuits are associated with hypo or hyperphagia and disruptions in heat production. Modern society is marked by high consumption of ultra-processed foods, rich in calories from fat and sugar, and sedentarism, the most significant factors driving the world toward an obesity pandemic and its various associated comorbidities.

Among the peripheral signals that act in the hypothalamus to control appetite and satiety, leptin and insulin stand out as hormones with potent anorexigenic effects. The binding of leptin to its specific receptor (ObR) activates several intracellular signaling pathways, including Janus kinase 2 (JAK2)/signal transducers and activators of transcription 3 (STAT3). STAT3 migrates to the cellular nucleus inducing POMC gene transcription (73). Regarding insulin signaling, this hormone activates the insulin receptor tyrosine (IR) kinase activity, which phosphorylates and recruits different substrate adaptors such as insulin receptor substrate1/2 (IRS1/2) proteins. Once activated, phosphorylated IRS displays binding sites for several signaling molecules, among them, phosphatidylinositol 3-kinase (PI3K), which has a significant role in insulin action, mainly via protein kinase B (Akt) activation (134). In the hypothalamus, activated Akt induces phosphorylation and deactivation of the Forkhead Box O1 protein (FoxO1).

Interestingly, FoxO1 is a transcription factor that is located at the cellular nucleus, inducing the transcription of several genes, including NPY. Once phosphorylated by Akt, FoxO1 leaves the nucleus and stops NPY transcription (73, 134). There is also cross-talk between the leptin and insulin signaling pathways in the hypothalamus, when leptin, through JAK2, also activates PI3K. This redundant process demonstrates the ability of neurons to use different strategies to control food intake (167). The inflammation induced by obesity or by high saturated fat intake disrupts these subtle signaling interneuronal connections, affecting the energy homeostasis and increasing food intake and body adiposity.

INFLAMMATORY MECHANISMS AND HYPOTHALAMIC DISORDERS

The chronic and low-grade inflammatory process is recognized as the main link between obesity and intracellular resistance to insulin and leptin signaling in hypothalamic neurons. The unveiling of this interplay started with an experimental study demonstrating that rodents chronically exposed to a high-fat diet exhibited a consistent immune response in the hypothalamic tissue, marked with increased gene expression and protein content of proinflammatory cytokines including TNF-α (tumor necrosis factor-alpha) and interleukin 1β (IL-1β) (2). Recent studies indicate that the inflammatory process induced by saturated fatty acids is initiated in non-neuronal cells, such as astrocytes (27, 46) and microglia (162, 163), subsequently extending the damage induced by inflammatory signaling to neurons. Inflammatory signaling in hypothalamic neurons results in the activation of serine kinases, including JNK (c-Jun N-terminal kinases) and IKK (inhibitor of kappa kinase), which are capable of negatively interfering with the leptin and insulin signals and their anorexigenic actions in neurons, contributing to hyperphagia and weight gain (19, 174). In both animals and humans, a few days of consuming a high-fat diet are sufficient to trigger the inflammatory process in hypothalamic cells (151). Also, these effects can be observed in other regions of the brain, such as the hippocampus (102).

In humans, the findings on obesity-associated hypothalamic inflammation are still discreet, as post-mortem studies are scarce and do not necessarily show the molecular mechanisms mainly due to the need for fresh tissue. In the last decades, analyses of cerebrospinal fluid (CSF), which is in direct contact with the CNS subareas, and magnetic resonance imaging, have helped to highlight inflammation, hypothalamic dysfunction, and also tissue degeneration in obese individuals. In 2003, Stenlöf *et al.* showed, for the first time, the inverse correlation between IL-6 levels in CSF and the weight and body fat of overweight or obese individuals (147). Moreover, van de Sande-Lee *et al.* (164) verified an increase in IL-6 and IL-10 levels in the CSF of subjects eight months after bariatric surgery. In the same study, when compared to lean individuals, morpho-functional analyses demonstrated that the hypothalamus of obese individuals presents functional changes, such as a reduced neuronal firing rate. In response to dextrose solution ingestion, lean individuals were more sensitive and had higher neuronal activity than obese individuals before and after bariatric surgery. The significant loss of body fat after bariatric surgery partially recovered neuronal firing in regions adjacent to the hypothalamus (164). Also, individuals with higher sensitivity to cerebral insulin, which was assessed by functional magnetic resonance imaging in response to nasal spray treatment, have a better response and weight reduction to an intervention program involving lifestyle modification (66).

Besides insulin and leptin resistance, the inflammatory process can chronically trigger pro-apoptotic signals in hypothalamic neurons in rodents, which are mainly concentrated in POMC neurons (74, 92). Although the verification of apoptotic signal markers in the human hypothalamus is a non-realistic strategy, Thaler and colleagues have established an indirect way of observing the hypothalamic damage in obesity, marked by gliosis, through functional magnetic resonance imaging (fMRI) analysis (151). Interestingly, this study showed that the gliosis associated with obesity was restricted to the hypothalamus and did not occur in different CNS areas. Furthermore, hypothalamic gliosis signals have also been found in obese children, followed by less hypothalamic activation in response to glucose intake (135). It should be noted that not all forms of obesity require hypothalamic gliosis. Gao and colleagues showed that leptin-deficient *ob/ob* mice become extremely obese on a standardized chow diet without gliosis. However, exposure to a high-fat diet increased inflammation and microglial activity, suggesting gliosis (39). Altogether, these data strongly suggest that human obesity is associated with neuronal lesions in the hypothalamus.

The most recent scientific evidence has shown that neurons do not suffer inflammatory damage directly from saturated fatty acid overload. High saturated fat concentrations reach the hypothalamus by crossing the blood-brain barrier in a specific region controlled by tanycytes (4). These fatty acids are recognized by astrocytes, which, after being sensitized, project signals through dendritic connections to the native microglial cells (18). On the microglia cell surface, TLR2/4 (toll-like receptor 2/4) is activated, firing proinflammatory intracellular signaling. After that, the inflammatory process

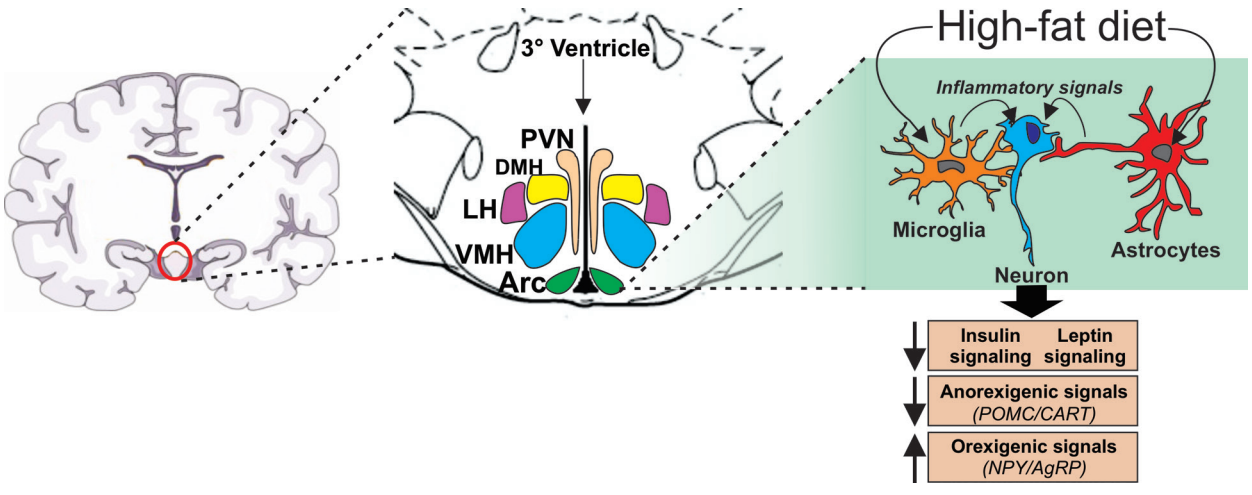

Figure 1. Schematic view of hypothalamic nuclei and the role of microglia and astrocytes in neuroinflammation. Inflammatory signals impair insulin and leptin pathways in hypothalamic neurons.

increases robustly, where microglial stimuli act directly in the neurons, beginning neuronal inflammation (4) (Figure 1). Although the neurons tolerate the inflammation for some time, the apoptotic signals in them are increased in a time-dependent manner (92).

Therefore, the development of strategies to attenuate the inflammatory process at a central level can be considered promising in the fight against obesity. In this sense, several studies have addressed the effects of physical exercise on the attenuation of inflammation, as well as insulin and leptin resistance in the hypothalamus and its impact on food intake control. Next, we will describe and discuss the main findings in this research field, involving studies with experimental and human models.

PHYSICAL EXERCISE AND FOOD INTAKE CONTROL

In the 1950s, the first studies appeared to determine the influence of physical exercise on energy expenditure and food intake. Initially, it was considered that food intake would be higher after physical activity, compensating for the exercise-induced energy expenditure (84, 156). Also, obesity, especially of a hereditary nature, was recognized as a result of voluntary activity reduction, impacting obesity etiology significantly (83). However, in 1953, Mayer showed less weight gain in genetically susceptible mice after exercise (83). These findings prompted the search for knowledge to understand whether the effects of physical exercise on body weight are exclusively achieved due to increased energy expenditure or are also related to reduced food intake. The study of King and colleagues was relevant in demonstrating that exercise has an anorexigenic effect, even in lean individuals (62). The work of Ropelle and co-authors was consistent in explaining that circulating factors from skeletal muscle in response to exercise would have an impact on reducing hyperphagia in obese rodents (124).

Although these studies were fundamental for advancing the knowledge regarding the mechanisms that regulate physical exercise-induced food intake control, we still have many challenges ahead. Indeed, several factors influence the effects of exercise on food intake, and this phenomenon is even more complicated when humans are investigated since energy intake can be mostly influenced by appetite, which is affected by numerous physiological, psychological, behavioral, and sociocultural factors (71, 142).

In the next section, we will address the acute and chronic effects of physical exercise in overweight and obese individuals. We do not intend to exhaust the subject, but to present the latest data from well-controlled research that has sought to investigate the impact of exercise on energy intake and hormonal response related to appetite suppression in overweight and obesity conditions.

EFFECTS OF ACUTE EXERCISE ON FOOD INTAKE CONTROL

Human studies: Acute effects

The real impact of acute physical exercise on energy intake and satiety in overweight individuals remains inconclusive. However, the number of investigations reporting on the effects of exercise on the regulation of hunger in obese populations has grown in recent years, and well-conducted and controlled studies have indicated that physical exercise is capable of causing a reduction in energy balance, which is transient, as a result of its anorexigenic effect in obese individuals (25).

Although the currently available research techniques do not allow for an acute assessment of sensitivity to anorexigenic and thermogenic hormones (i.e., leptin and insulin) specifically in the hypothalamus, studies with overweight or obese humans have aimed to support the evidence. Thus, several works have evaluated the serum levels of appetite-related hormones in response to physical exercise, including the orexigenic hormone (acylated ghrelin), and the anorexigenic hormones peptide tyrosine-tyrosine (PYY) and glucagon-like peptide-1 (GLP-1), as well as the circulating levels of leptin and insulin, among others (11, 25, 26, 54, 160), before, during, and after exercise. Also, fMRI allows us to understand the blood fluxes into the brain, specified by region, with realistic images in real-time.

For example, when evaluating how 30 minutes of aerobic exercise sessions could reduce stress behavior, Zschucke and colleagues showed that improved stress response was not associated with low levels of cortisol and α-amylase after exercise, but positively associated with a high bilateral hippocampus response. Both the hippocampus and the prefrontal cortex are intimately involved in hypothalamus-pituitary-adrenal (HPA) axis negative feedback (177). Several brain regions are involved in the downregulation of HPA axis activity, and when the paraventricular nucleus initiates the neuroendocrine signaling cascade of the HPA axis, it receives mostly inhibitory input from the hippocampus, the anterior cingulate cortex, and the prefrontal cortex (52). In contrast, the amygdala exerts a mostly excitatory effect on the paraventricular nucleus. All these areas are integrated by neuronal projections, which directly influences the hypothalamus (52, 86). It has been demonstrated that there is a complex circuitry at the central level that participates in the hypothalamic responses of hunger control. This research field still needs further advances.

Several studies have evaluated the impact of acute exercise sessions on eating behavior in overweight and obese subjects, from both sexes (26, 132), among adolescents (152, 155), and among young or middle-aged individuals (26, 160), in activities, such as cycling (160), running (26), or other continuous types of moderate or high-intensity exercise (54, 132, 140, 159, 160), using measurements of circulating insulin or leptin levels (79, 159). Based on this set of studies, some of which were very well controlled, we can present essential characteristics of the interference of exercise in the modulation of appetite in overweight individuals, in a debate that becomes more robust when associated with other studies with mechanistic evidence.

Ueda and coworkers showed that 1 hour of cycle ergometer exercise at 50% of maximal oxygen uptake (VO_2max) enhances the PYY and GLP-1 plasma levels in young adult obese individuals [age: 22.93 ± 4 yr; BMI (body mass index): 30.0 ± 3.1 kg.m^2], indicating that these satiety signals may play a role in acutely regulating appetite and energy homeostasis (160). Also, the effect of exercise in reducing caloric intake in overweight individuals was higher than in eutrophic individuals (160). Douglas *et al.* verified similar responses in overweight

and obese adult women and men (age: 45.0 ± 12.4 yr; BMI: 29.2 ± 2.9 $kg.m^{-2}$), who performed moderate-intensity exercise (60 min/60% peak VO_2) on a treadmill (26). The authors attributed the temporary suppressive effects of exercise on food intake to an increase in the circulating concentration of PYY and GLP1, without further compensatory changes in appetite (26).

After investigating the acute effects of continuous (1h) and intermittent (12 sessions of 5 min, totaling one hour) treadmill exercise performed at moderate intensity (60–65% VO_2 peak) in young obese women and men (age: 18–35 yr; BMI: 30.0 kg.m2), Holmstrup and coworkers reported that serum PYY levels did not change over 12 hours of continuous or intermittent exercise. However, the authors observed that intermittent exercise induced satiety more significantly than a continuous exercise in obese individuals (55). Also, Sim *et al.* compared the acute effects of continuous moderate-intensity cycling exercise (MC = 60% VO_2 peak), high-intensity intermittent cycling exercise (HI = alternating between 60 s at 100% of VO_2 peak and 240 s at 50% of VO_2 peak), and very high-intensity intermittent cycling exercise (VHI = alternating between 15 s at 170% of VO_2 peak and 60 s at 32% of VO_2 peak) in overweight and sedentary young adult men (age: 30 ± 8 yr; BMI: 27.7 ± 1.6 $kg.m^2$) and verified that food intake was lower in the HI and VHI sessions compared to the MC session (140). Furthermore, the subsequent energy intake remained lower in the participants who performed the VHI exercise compared to the control group. There was also a reduction in the levels of active ghrelin after VHI exercise when compared to other types of exercise.

Interestingly, Holliday and coworkers evaluated the effects of low-volume and high-intensity cycle ergometer exercise (4 sprints of 30 s) on appetite and gastrointestinal hormones (ghrelin and GLP1) in overweight women and men (age: 34 ± 12 yr; BMI: 27.7 ± 1.7 $kg.m^2$). The authors observed that exercise-induced appetite suppression was accompanied by a reduction in acetylated ghrelin and a modest increase in circulating GLP1 (54). The answers found regarding the variables involved in food intake control are certainly not always unanimous. For instance, Nyhoff and coworkers found no changes in GLP1 in obese women (Age: 24.3 ± 4.6 yr; BMI: 37.3 ± 7.0 $kg.m^2$) after running exercise on a moderate-intensity treadmill (55% of VO_2max) or high-intensity interval exercise (4 min at 80% of VO_2max and 3 min at 50% of VO_2max) (105). There was no difference in the concentration of GLP1 between the types of effort during the exercise, but there was during recovery. Also, the insulin concentration was reduced during the meals that followed the exercise; however, the intensity of the exercise had no impact on this response (105).

Tsofliou *et al.* evaluated the effects of moderate exercise (20 min brisk walking) in obese adult women (age: 50.0 ± 8.5 yr; BMI: 37.27 ± 6.5 $kg.m^2$) and observed a reduction in appetite and satiety (159). Interestingly, serum leptin levels were correlated with reduced hunger and satiety after the exercise intervention. Larsen and colleagues noted that acute high-intensity exercise, but not moderate-intensity exercise, reduced ghrelin levels in overweight men (69). This large body of evidence suggests that the relationship between exercise intensity and the secretion of appetite-suppressing gastrointestinal hormones requires further investigation to determine the mechanisms involved.

Regarding the effect of physical exercise on obese young people (obese adolescents), it has been reported that appetite is suppressed in subsequent meals. Thivel and colleagues elegantly showed that acute exercise does not affect energy intake in lean individuals, but reduces food intake in obese young people when performed at high intensities, without changing the macronutrient composition of the meal (153, 155). Said *et al.* demonstrated that an acute cycle ergometer session (70% of VO_2max for 40 min) reduced food consumption in the morning among obese girls (age: 13.7 ± 1.1 yr; BMI: 30.5 ± 3.4 $kg.m^2$) (125).

A recent study, which investigated the effects of high-intensity exercise (HIEX = three 10-minute sessions at 70% of VO_2peak at 60–70 rpm, with 1.5 min of active rest interposed at 25 W with 60-70 rpm) performed on a bicycle on appetite, hunger regulating hormones, and inflammation markers in obese boys (age: 10-18 yr; BMI: 15th – 85th BMI for age percentile) (56), showed a reduction in the levels of active ghrelin and an increase in IL-6. These findings were followed by an inverse correlation between IL-6 and appetite intensity. Altogether, the data suggest an association between increased levels of IL-6 through chronic exercise and reduced appetite in overweight and obese boys. However, this interpretation should be made with caution, as there was also a reduction in ghrelin levels and an increase in cortisol, which are hormones that are known to increase appetite (56).

Overall, the evidence shows that at least partial aerobic exercise acutely exerts a regulatory effect on hormones involved in food intake control, and consequently, this has been associated with a suppressive effect on appetite in overweight individuals (26, 131). On the other hand, studies using resistance exercise are limited. In one such study, Larsen *et al.* found that the levels of PYY and GLP-1 did not change after resistance exercise (10 sets of 8 repetitions of bilateral leg extension exercises at a resistance of 75% of 1RM with 150 s recovery between sets) in overweight men (age: 48 ± 5 yr; BMI: 29.9 ± 1.9 kg m^2) (70). However, more research evaluating the acute effects of resistance exercise in its different forms of execution (concentric, eccentric, and isometric) on individuals with varying degrees of obesity and age (especially older generations) is still needed.

RODENT STUDIES: ACUTE AND SHORT-TERM EFFECTS AND PROPOSED MECHANISMS

Improvement of hypothalamic insulin and leptin sensitivity

Experimental models in research have been essential for assessing the effects of acute or short-term physical exercise in controlling food intake. Some studies have contributed by elucidating the mechanisms responsible for the improvement of insulin and leptin signaling in the hypothalamus after acute exercise. Gaspar *et al.* showed that a single session of exercise increased the hypothalamic protein content of adaptor protein containing the pleckstrin homology domain, the phosphotyrosine-binding domain, and leucine zipper motif 1 (APPL1) in high-fat diet-induced obese mice (41). It is known that APPL1 can bind to Akt (41), improving its phosphorylation at serine 473, as well as enhancing leptin signaling in specific cell types (24). On the other hand, Gaspar and coworkers observed a reduction in the protein levels of the mammalian

homolog of Drosophila tribbles protein 3 (TRB3) (41), a negative regulator of Akt activity (28), in the hypothalamus of exercised obese mice. These results suggest that acute exercise can stimulate the production of proteins that interact directly with insulin and leptin signaling in the hypothalamus, increasing the anorexigenic signals of these hormones.

Another impressive effect that could explain the transient improvement in insulin and leptin signaling in the hypothalamus is the acute anti-inflammatory effect of exercise. For instance, acute moderate-intensity swimming or treadmill exercise was sufficient to reduce IKK phosphorylation and endoplasmic reticulum stress in the hypothalamus of obese rats (124). The reduction in inflammation was associated with an increased response to insulin and leptin in the hypothalamus of these rats. After the acute exercise session, a significant improvement was observed in insulin (IRS/PI3K/Akt pathway) and leptin (JAK2/STAT3) signal transductions in the hypothalamus, which was accompanied by the modulation of neuropeptides such as POMC and AgRP, resulting in less food intake (124). However, the question is: how could acute physical activity change the inflammatory status in hypothalamic neurons?

IL-6 is an intracellular signaling molecule associated with extensive immune responses in several conditions (146). Also, IL-6 can be produced and released by skeletal muscle (hence the name myokine) in response to physical exercise, performing pro- and anti-inflammatory actions depending on the concentration and circumstances of the target tissue (110, 146). Exercise-induced muscle contraction leads to IL-6 mRNA expression and its transcription (109). During physical exercise, this myokine is released into the circulation, which can influence metabolism and modify the production of other cytokines in tissues and organs (110). Interestingly, IL-6 knockout mice develop obesity prematurely, highlighting the importance of this molecule in controlling energy homeostasis (168).

Besides being released by skeletal muscle during contraction, IL-6 can be produced in response to exercise directly in the CNS. Nybo *et al.* observed increased brain levels of IL-6 in healthy subjects after two sets of aerobic exercise on a cycle ergometer (104). Similar findings were verified in animal models. Silva and coworkers showed high levels of IL-6 in the hypothalamic tissue of exercised mice (138). Matsumoto and coworkers suggested that the enhanced hypothalamic levels of IL-6 occur due to positive feedback generated by the peripheral increase in this cytokine (82). They injected recombinant IL-6 into rats intraperitoneally and observed an increase in the protein content of IL-6 in the hypothalamus (82). Goldfish performing a short exercise protocol displayed lower food intake and high levels of IL-6 in both skeletal muscle and hypothalamic samples (101), suggesting that this is a conserved physiological mechanism among different species. Furthermore, Aniszewska and colleagues clearly showed that forced acute swimming exercise led to high levels of IL-6 in the microglia, astrocytes, and neurons of mice (3). So, how can we explain the anti-inflammatory effects of IL-6?

Exercise-induced IL-6 release may lead to systemic anti-inflammatory responses (103, 110) through the modulation of soluble TNF-α receptors, as well as the increase of IL-1 receptor antagonist (IL-1Ra) and mainly IL-10, which can inhibit the phosphorylation and activity of the IKK complex, as well as nuclear factor kappa B DNA binding (130). Interestingly, the disruption of IL-10 synthesis by using an antisense oligonucleotide against IL-10 in the hypothalamus of obese rats abrogated the anti-inflammatory effects of acute exercise or those of IL-6 recombinant intracerebroventricular injection in obese animals (124). The IL-6/IL-10 axis-generated anti-inflammatory mechanism could contribute to insulin and leptin sensitivity improvement in hypothalamic neurons, reestablishing the anorexigenic and thermogenic signals, and finally, committing to the maintenance research has shown that increased IL-6/IL-10 levels can contribute to the control of energy homeostasis (124, 164), further studies are needed to expand the knowledge regarding this mechanism.

Altogether, the results obtained suggest that acute exercise induces an anti-inflammatory response, which is accompanied by an increase in insulin and leptin sensitivity in the hypothalamus of obese rodents. Also, this anti-inflammatory effect observed after acute exercise appears to be partially related to the central role of IL-6 in the hypothalamus. Figure 2 illustrates the effects of acute exercise on the hypothalamus and hunger control in humans and animals.

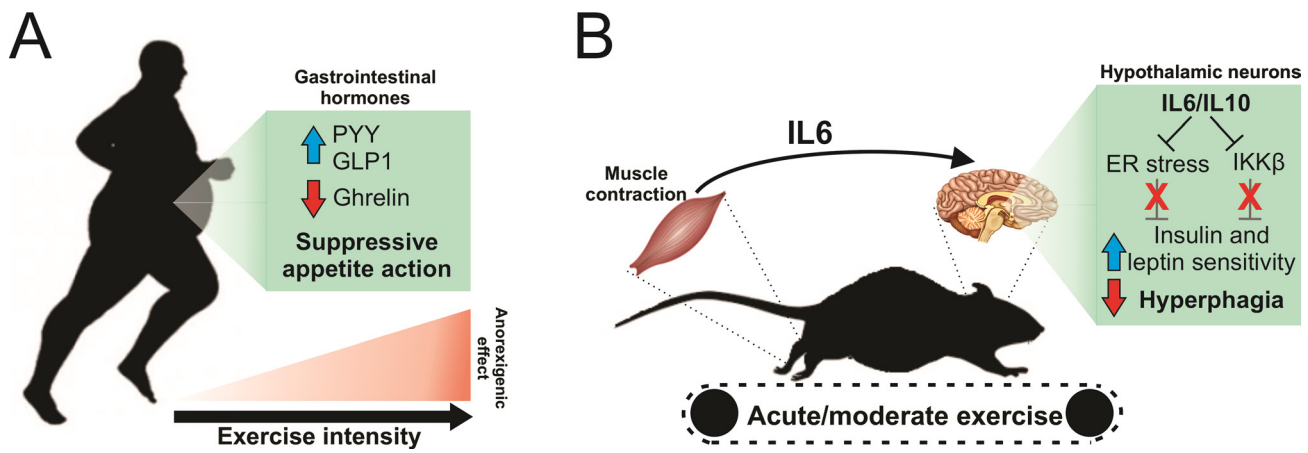

Figure 2. Effects of acute exercise in the control of food consumption. A. Acute exercise modulates gastrointestinal hormones and suppresses appetite in humans in an intensity-dependent manner. B. Muscle contraction increases circulating IL-6 levels. IL-6 elicits an anti-inflammatory action in hypothalamic neurons, improving insulin and leptin signaling in rodents.

EFFECTS OF CHRONIC EXERCISE ON HYPOTHALAMIC INFLAMMATION AND FOOD INTAKE CONTROL

Human studies: Chronic effects

There are still a limited number of studies addressing the impact of chronic physical exercise on appetite and hunger-regulating hormones in obese humans. These studies have examined the effects of physical training on sedentary, overweight, and obese individuals, highlighting different appetite responses when comparing inactive with trained subjects. The evidence regarding the impact of physical training on the plasma levels of satiety-related peptides is also controversial and relatively scarce, particularly in a population that is overweight.

Martins and coworkers investigated the effects of medium-term exercise treadmill walking or running (12-week supervised exercise program/five times per week, at 75% maximal heart rate) on body weight, fasting/postprandial levels of orexigenic and anorexigenic hormones, as well as subjective appetite sensations in sedentary overweight/obese subjects (age: 36.9 ± 8.3 yr; BMI: 31.3 ± 3.3 kg/m^2) (77). The authors verified a significant decrease in body weight and fasting insulin, as well as an enhancement in acylated ghrelin plasma levels and fasting hunger state. Also, a moderate rise in the release of GLP1 was described after exercise, as well as a significant increase in acylated ghrelin postprandial suppression. These findings suggest that exercise-induced body weight reduction can enhance the desire to eat during fasting conditions but seems to be counterbalanced by an improvement in appetite control sensitivity (77). On the contrary, obesity is associated with increased levels of plasma ghrelin (17). Overweight subjects performing aerobic and resistance exercise for 12 months significantly reduced their body weight, adiposity, and circulating leptin levels (158). According to a systematic review and meta-analysis of randomized controlled trials, chronic physical exercise lasting two weeks or more is related to reduced leptin levels in children up to the age of 18 years with a body mass index higher than the 95th percentile for age and sex (32).

Martins and colleagues analyzed obese individuals (age: 33.4 ± 10.0 yr; BMI: 32.3 ± 2.7 kg.m^2) subjected to isocaloric exercise sessions (250 kcal), on a high-intensity interval cycle ergometer (85%–90% HRmax and work/rest ratio of 8/12 s) or on a moderate-intensity continuous cycle ergometer (70% HRmax), and short-term exercise (125 kcal), performed three times per week for 12 weeks and verified that insulin levels were reduced and GLP1 levels were increased during all exercise sessions when compared to individuals at rest (60). The acetylated ghrelin values were lower for continuous and high-intensity exercise, but not for short duration exercise when compared to the control group. Plasma PYY levels and energy intake did not differ between interventions (76). In a study involving overweight and obese men and women (age: 39.6 ± 9.8; average BMI: 31.8 kg.m^2), it was shown that 12 weeks of aerobic training (approximately 70% of each individual's maximum heart rate 5 d/wk) augmented fasting hunger but also increased the satiety response to a fixed meal (63).

Adiposity reduction-induced anti-inflammatory response is another significant impact of performing physical training. A large body of evidence shows that chronically different types and intensities of physical exercise reduce serum and tissue inflammatory markers (5, 40, 103, 121). Elder and colleagues reviewed the effects of various amounts of physical activity on body fatness, energy intake, and food preferences in humans, and concluded that physical training has a consistent impact on body fat percentage, which is caused by increased energy expenditure, however, without changing eating behavior (31). Also, previous studies suggest that individuals with higher pre-training adiposity show more significant changes in appetite and gastrointestinal hormones (93, 114). Gibbons and colleagues demonstrated that overweight individuals (age: 18-55 yr; BMI: 27-34.9kg / m^2) presenting more significant reductions in adiposity after an aerobic exercise intervention of 5 sessions/ week at moderate intensity (70% of maximal heart rate) for 12 weeks also exhibited a more pronounced postprandial increase in GLP1 and PYY hormones, as well as a reduction in acetylated ghrelin levels compared to individuals who lost less weight (42).

In a recent systematic review and meta-analysis, Taylor *et al.* compared the chronic effects (i.e., four weeks or more) of high-intensity interval training and sprint interval training on energy intake with moderate-intensity continuous training or no exercise conditions (150). Despite the considerable heterogeneity of the findings, there was no compensatory enhancement of energy intake in response to high-intensity interval training and sprint interval training compared to moderate-intensity continuous training or no exercise. Nevertheless, the inclusion of the participants' adherence to exercise programs, individual food preferences, and psychological parameter measurements was highlighted by the authors as being essential methodological considerations to be included in future investigations (150).

Although the following hypothesis must be experimentally confirmed, physical training effects could also cause an anti-inflammatory response in the hypothalamic nuclei of obese individuals, restoring satiety signals. It is essential to point out the contradictions in the literature regarding how appetite is influenced by the type, duration, or intensity of exercise in humans. Also, the characteristics of the subjects (i.e., body fat percentage, initial fitness level, age, or gender) may contribute to the data discrepancies in the literature. The difference in the responses is more pronounced when analyzing the effects of exercise on appetite in athletes of different sports (44, 125, 127), thus hampering interpretations of the data. Other issues, such as the impact of concentric or eccentric contractions, have been investigated, providing more information within the scope of exercise sciences and hunger control (154). Thivel and coworkers showed that eccentric cycling during a multidisciplinary weight loss intervention might prevent adolescents with obesity from increasing their food intake (108). The amount of studies looking at the responses of food intake and metabolic parameters to physical exercise performed at different times of the day has also been increased (34, 128). It is important to note that the chronic exercise-induced body fat reduction hampers the interpretation of the isolated beneficial effects of exercise since the reevaluations are performed under indirect actions of exercise, mainly related to adiposity loss.

Another interesting point of view concerns the impact of physical exercise on energy homeostasis with advancing age. It is well established that senescence is associated with increased proinflammatory markers, such as circulating levels of IL-6 and TNF-α, a new phenomenon known as "inflammaging." Therefore, the effects of physical exercise on energy control during the aging process need to be better elucidated (1, 87). Also, inflammatory responses and cytokine secretion during

advancing age are influenced by fat mass depots and adherence or not to physical exercise (1, 45). Physical activity can contribute to metabolic health in aging through reducing body weight (48), proinflammatory cytokines (1), and TLR-4 signaling (122), as well as preventing the accumulation of senescent T-cells (90), hemodynamic improvement, anti-atherogenic actions, and oxidative stress attenuation (47, 170). However, it is necessary to assess whether the anti-inflammatory effects of exercise also occur in the hypothalamus, benefiting calorie intake during the aging process. Furthermore, the impact of physical exercise throughout life has been shown to be positive, culminating in lower levels of proinflammatory cytokines and higher levels of anti-inflammatory cytokines (89, 91).

Recently, it was reported that the success of lifestyle changes (i.e., increased physical activity, as well as reduced-fat consumption, and high fiber diet) in reducing total and visceral adiposity is more significant in obese individuals with high sensitivity to brain insulin, which was assessed by fMRI after nasal spray administration of insulin (66). Also, higher susceptibility to brain insulin is associated with lower fat regain during a 9-year follow-up period (66). Heni *et al.* reported that lean young individuals with high sensitivity to hypothalamic insulin showed an improved second phase of insulin secretion by pancreatic cells, positively impacting the organism (51). On the other hand, the obese subjects with hypothalamic insulin resistance did not present the same response and showed negative impacts on metabolic control, highlighting that the maintenance of the central response to insulin may be a pivotal point in obtaining more robust responses of physical exercise to food intake. Future research involving the obese population may lead to new insights into this phenomenon.

Although there is no evidence of a direct anti-inflammatory effect on the hypothalamic tissue of humans, there are a large number of studies reporting that physical exercise increases the circulation of anti-inflammatory factors (IL-6 and IL-10) and decreases proinflammatory factors such as TNF-α and IL-1β, among others, which are found to be elevated in obese individuals (65, 149). The anti-inflammatory effects of exercise are associated with weight loss and hormonal regulation, such as increased insulin sensitivity and increased adiponectin, with metabolic health-promoting repercussions (65, 116, 117, 157). It should be noted that responses to exercise can be different depending on health conditions, cytokine profile, the period after the stimulus when the analysis is performed, and characteristics of the effort made (type and intensity of exercise practiced) (65, 116, 117, 157).

Rodent studies: Chronic effects and hypothalamic molecular analyses

Obese rodents performing voluntary aerobic exercise for eight weeks showed a significant reduction in adiposity (8). Despite the decrease in plasma leptin concentrations, there was no increase in food intake as a compensatory mechanism. Furthermore, a reduction in NPY orexigenic peptide expression was observed in the hypothalamic ventromedial nucleus of these animals (8). Similar evidence was found in obese mice performing voluntary exercise for 12 weeks that showed increased sensitivity to insulin and leptin in the hypothalamus (68). These results were accompanied by increased expression of POMC and reduced adiposity (68). Another interesting study showed that aerobic training could mimic leptin effects by increasing Jak2 and STAT3 phosphorylation in the hypothalamus of rats, even with low levels of leptin (175).

On the other hand, Borg and coworkers administered a high-fat diet for 12 weeks to mice and subjected them to an aerobic physical training protocol in the last 6 weeks of the dietetic treatment. The authors found no change in leptin sensitivity and caloric intake in obese animals (10). It is necessary to report that these responses related to improved leptin signaling at the central level are not unanimous, reinforcing the urgency for further studies. The anti-inflammatory effects of chronic exercise on the CNS, including the hypothalamus, appear to be more consistent and long-lasting when compared to acute exercise.

Physical training can prevent hypothalamic inflammation induced by a high-fat diet. Yi *et al.* demonstrated lower microglia activity in exercised animals, marked by a decrease in Iba1 (allograft inflammatory factor 1) (172). Silva and coworkers showed that aerobic training reduced transforming growth factor-beta 1 (TGF-β1) protein content and nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor-alpha (IkB-α) phosphorylation in hypothalamic tissue in middle-aged obese mice (137). These data were accompanied by an increase in energy expenditure, as well as a reduction in both body weight and accumulated food intake. However, it is important to note that, chronic excessive exercise can promote hypothalamic tissue inflammation in healthy mice, highlighted by the upregulation of IL-1β, TNF-α , and JNK phosphorylation (111). Similar findings were described by Pinto and coworkers, who observed that chronic/intense exercise led to endoplasmic reticulum stress markers in the hypothalamus (115). Therefore, the anti-inflammatory effects of physical exercise on the CNS seem to be dependent on the balance between training load and an adequate recovery period.

Another important study demonstrated that repeated bouts of high-intensity physical exercise were sufficient to promote a rapid reorganization of synaptic signals in NPY/AgRP and POMC neurons in the arcuate nucleus of the hypothalamus of mice, concomitantly with a reduction in food intake (50). Recently, the protective effect of physical exercise on neuronal apoptosis in obese animals has been addressed (74). Obese mice receiving a fat-rich diet and performing an endurance exercise protocol for eight weeks showed increased hypothalamic levels of IL-10 and B-cell lymphoma 2 (Bcl2), with more effective anti-apoptotic action, as well as reduced BCL2-associated X protein (Bax), a potent pro-apoptotic protein. These molecular responses were accompanied by increased leptin sensitivity and reduced food intake (74). Nevertheless, the number of studies evaluating the hypothalamic apoptotic process in response to physical exercise is still limited.

On the other hand, Kim and colleagues evaluated the effects of aerobic physical training on short-term memory and the hippocampus apoptotic pathways of rats with traumatic brain injury (59). The authors observed attenuation of short-term memory impairment, as well as a decrease in DNA fragmentation, marked by reduced caspase-3 protein content in the hippocampus of the mice. Also, a 10-day treadmill exercise protocol increased the Bcl-2 content in the hippocampus of rats (59), suggesting that physical exercise may prevent traumatic brain injury-induced apoptotic neuronal cell death and allow the partial recovery of short-term memory.

Altogether, the human and animal studies have demonstrated that the effect of chronic exercise on the control of food consumption is still controversial; however, exercise training is associated with lower adiposity and inflammatory markers. Animal models of obesity have demonstrated that exercise training prevents or reduces high-fat diet-induced hypothalamic inflammation and neuronal damage induced by apoptosis. Figure 3 illustrates the effects of chronic exercise on the hypothalamus and hunger control in humans and animals.

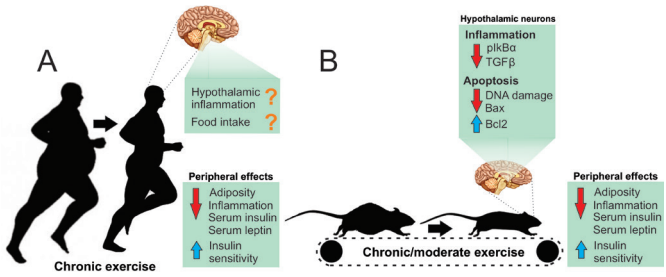

Figure 3. Effects of chronic exercise in the control of food consumption. A. Exercise training reduces the body weight and multiple benefits in peripheral metabolism, but the effects in the control of food consumption are controversial. B. Chronic exercise reduces hypothalamic inflammation and neuronal apoptosis in rodents.

OTHER MECHANISMS WITH A POTENTIAL REGULATORY EFFECT OF FOOD INTAKE AND ENERGY EXPENDITURE IN RESPONSE TO EXERCISE

In the last decades, there has been a growing understanding of the integration between organs and systems, especially among those with a crucial role in controlling energy metabolism. In this context, the intestinal microbiota (also known as the microbiome) regulates metabolic pathways of the host, with several connections established as a new axis with other tissues such as muscle and brain (36). These microbial products from the intestine also influence the endocannabinoid system (ECS). Through a vast and complex network of lipid and protein mediators, they have an important influence on the functioning of organs, tissues, and body metabolism (36). Both the microbiota and the ECS are strongly influenced by lifestyle and food patterns.

The gut-brain axis mechanistic studies showed the diversity of interactions modulating the hypothalamus through vagal nerve stimulated by GLP1, fatty acids, and, recently, agonists for ECS or its analogs, impacting the control of food intake and energy expenditure. Short-chain fatty acids (SCFAs) (64), lipopolysaccharide (LPS) (161), glutamate and γ-aminobutyric acid (GABA) (85), and other microbial products present at the intestinal lumen act as bidirectional messengers at the gut-brain axis. Some microbial products reach the brain during dysbiosis conditions, interfering with the neuronal circuits (36). High levels of LPS that cross the blood-brain barrier (BBB) (120) inducing TLR-4-dependent proinflammatory responses in the microglia, which are associated with the activation of inflammatory cytokines and resistance to leptin and insulin directly in hypothalamic neurons. Endotoxemia causes damage in both the intestine and brain, raising systemic and cerebral inflammatory mediators (IL-1β, TNFα, and IL-6), associated with gliosis signs in hypothalamic areas responsible for controlling energy balance and maintaining body weight (36, 57, 126, 171). Also, studies in recent years have shown that some commensal bacteria produce endocannabinoid (eCB)-like metabolites functioning in the same receptors and cells as the host (36).

Current data indicate an essential link between obesity development and disorders in the ECS in different tissues involved in regulating metabolism (21, 80, 106, 139). Hyperactivity of ECS is characterized by an increase in the concentration of eCB (such as N-arachidonoethylamine [anandamide, AEA] and 2-arachidonoylglycerol [2- AG]), modification of the expression of cannabinoid receptors (CB1R and cannabinoid type 2 (CB2R), and alterations in crucial enzymes involved in the biosynthesis and degradation of eCB acid amide hydrolase (FAAH, the enzyme that degrades AEA) and N-acylethanolamines (NAEs, AEA counterparts) are generally evident during the development of obesity (21, 80, 106, 139). In the hypothalamus, endocannabinoids are involved with increased orexigenic neuropeptides and decreased anorectic neuropeptides (15, 22). CB1R deficient mice are hypophagic, lean, sensitive to insulin, and are protected from diet-induced obesity (15, 119). In genetic models of obesity (Zucker fa/fa rats and ob/ob and db/db mice) with an interruption in leptin signaling, high hypothalamic levels of endocannabinoids were observed compared to wild-type animals (106). Studies with obese humans have found ECS dysregulation with higher AEA and 2-AG in plasma and adipose tissue (6, 23). The increase in 2-AG levels in obese rodents seems to be related to leptin signaling deficiency (21). Di Marzo *et al.* were pioneers in reporting that intravenous leptin injection decreases hypothalamic levels of AEA and 2-AG in rats (21). However, other hormones such as ghrelin and glucocorticoids have also been indicated as critical agents for increasing the levels of endocannabinoids and inducing hypothalamic dysregulation in obesity (16, 29).

Strategies aimed at changing lifestyle with effects on the intestinal microbiota and the ECS may represent a safer alternative than pharmaceutical approaches (20). Data obtained through experiments with rodents demonstrated that physical exercise alters the composition of the intestinal microbiota (2, 14, 100, 112, 129). Rats submitted to physical exercise showed an increase in n-butyrate. It was also observed that the total distance covered by these animals correlates inversely with the Bacteroidetes-Firmicutes ratio (81). Obese Zucker (fa/fa) rats under moderate-intensity running training had altered the composition and diversity of its intestinal bacteria, similarly to that of their non-obese congeners (113). Human studies have also shown positive effects of physical exercise on the microbiota. It was seen that an aerobic physical training program with brisk walking for 12 weeks increased the content of Bacteroides spp in sedentary older women (94). Reinforcing these findings, Allen *et al.* (2) found that obese and lean individuals had different intestinal microbiota compositions at the beginning of the study. After 6 weeks of endurance exercise training, this difference disappeared. It was further observed that SCFAs concentrations increased in lean individuals. Such an attempt at analogy and interpretation of the data can be reinforced by a study investigating the effects of the participation of overweight sedentary women in an aerobic exercise program (exercise bike, three times a week, for six weeks) (100). The authors found that physical

exercise increased the relative abundance of the genera Verrucomicrobia and Akkermansia and decreased the number of proteobacteria associated with inflammation in the intestine. A previous study found a reduction in the Firmicutes/Bacteroidetes ratio in patients with pre-diabetes and type 2 diabetes mellitus (DM2) in response to both sprint interval training and moderate-intensity continuous training program (99). Furthermore, both training programs reduced systematic and intestinal inflammatory markers (TNF-α and LPS) (99). Although the evidence points to positive effects of physical exercise on the microbiota, it is relevant to document that the adaptations obtained seem to be reversed after the discontinuity of training (2). Otherwise, forced and exhaustive exercise can have a different impact than moderate exercise (173). In an experiment that sought to assess the effects of overtraining on an animal model, it was found that the diversity of the microbiota was reduced in mice (173).

The effects of physical exercise have also been promising in ECS. Elegantly, after submitting trained male university students to an acute treadmill running or cycling session (for 50 min at 70-80% of maximum heart rate), Sparling *et al.* showed for the first time that moderate exercise activates the ECS (144). Other studies that evaluated the acute effect of physical exercise in humans also found an increase in plasma levels of endocannabinoids (i.e., AEA) (53, 118). Interestingly, a study investigating the effects of 1 year of intervention with lifestyle modification, including physical activity in obese humans, found that this strategy induced a significant decrease in plasma AEA and 2-AG levels and fasting visceral fat (20). Gamelin *et al.* demonstrated that chronic aerobic exercise attenuates the CB1R gene induced by a high-fat diet in Wistar rats (38); however, the same study showed a high-fat diet combined with physical training did not affect AEA and 2-AG levels in the rats hypothalamus. Therefore, further studies about the impact of physical exercise on ECS, especially on the central nervous system, are needed. Discoveries in this area of knowledge will undoubtedly open new paths for future approaches involving microbiota, ECS, and physical exercise, which will allow advances and perspectives to combat disorders linked to obesity.

In addition to microbiota and the endocannabinoid system, accumulating evidence has demonstrated that resistin plays a critical role in controlling neuroinflammation and hypothalamic insulin and leptin resistance. Resistin is recognized as a hormone, and high levels of this substance are strongly associated with insulin resistance, DM2, cardiovascular diseases, and other metabolic abnormalities (98). It has been demonstrated that while resistin is mainly produced and secreted from adipose tissue of rodents (148), in humans, resistin is predominantly expressed in cells derived from the immune system, including macrophages and peripheral blood mononuclear cells (133). Resistin signaling remains unclear; however, it has been proposed that TLR-4 and adenylyl cyclase-associated protein 1 (CAP1) play a critical role in the resistin signaling transduction (107). Benomar and colleagues demonstrated that resistin binds to TLR-4 and elicits hypothalamic JNK activation and insulin resistance in rodents (7).

Conversely, the disruption of hypothalamic resistin signaling reduced several inflammatory markers and improved insulin sensitivity in rodents (123). Importantly, it has been nicely demonstrated that resistin controls the expression of leptin signaling components, including the leptin receptor and SOCS-3 in the arcuate nucleus of the hypothalamus (176). These studies collectively support the hypothesis that resistin is involved in controlling hypothalamic inflammation and insulin and leptin resistance, at least in rodent obesity models.

Physical exercise effects on resistin serum levels have been extensively investigated. While several studies reported that physical exercise modulates resistin serum levels in both mice and humans, other studies showed no alterations. Shirvani and colleagues reported that 6 weeks of eccentric training increased irisin and nesfatin-1 but reduced the resistin serum levels in rats (136). Curiously, Liu *et al.* reported that 8 weeks of aerobic exercise decreased serum resistin levels in diabetic (*db/db*) mice. Still, no alterations were observed in insulin resistance or glucose tolerance (72). However, Sousa *et al.* reported that 8 weeks of physical training reduced inflammatory markers but did not change the resistin levels of obese mice (143). These discrepant findings could be associated with the different exercise protocols, for instance, aerobic vs. resistance, 6wk vs. 8 wk, and moderate vs. intense. Furthermore, the animal models used in these studies were also different, including lean, obese, and obese/diabetic. Thus, further studies are required to define the effects of different exercise protocols in controlling resistin secretion in animal models.

The effects of physical exercise on resistin serum levels in humans have been investigated in the last decades, particularly in obese and type 2 diabetic patients. In 2007, Kadoglou *et al.* reported that 16 weeks of aerobic exercise training reduced the resistin serum levels in patients with DM2 (58). Furthermore, a multicentric study revealed that moderate to vigorous exercise training reduced resistin serum levels in humans, but was not associated with alterations in central adiposity (166). A similar result was observed in overweight and obese adults in response to 12 months of moderate exercise (43). Although several studies have demonstrated that chronic exercise may reduce the resistin levels in overweight, obese and diabetic individuals, a meta-analysis study revealed that exercise did not promote a significant reduction in resistin levels (49).

Furthermore, the impact of exercise on resistin serum levels was not observed after an acute session of high-intensity interval exercise in young overweight/obese women (165) or after high-intensity training in chronic obstructive pulmonary disease (35). Conversely, Fonseca and coworkers demonstrated that an acute session of exercise until fatigue increased serum resistin levels in sedentary but not in trained individuals (9). Although all of these studies evaluated the impact of exercise on resistin content in murine and humans, the precise implications involving the resistin signaling to the hypothalamus in response to physical exercise remains unknown and deserves further investigations.

CONCLUSIONS AND FUTURE DIRECTIONS

The effects of physical exercise on food intake control have been investigated over the last 70 years. Human and animal models have shown different outcomes due to the type of exercise (resistance, aerobic), modality (running, swimming, cycling), environmental characteristics (i.e., cold, heat, and hypoxia) (4, 10, 57), training load (i.e., frequency, volume, and intensity), and recovery intervals following exercise sessions, which could

have a notable impact on food intake and even on spontaneous activity (8, 17, 35, 39, 43, 84, 126), challenging the determination of food consumption in exercised individuals. Furthermore, the host factors (i.e., gender, lean, obese, age, etc.) seem to be critical. Chronic exercise induces an extensive modification in human metabolism, changes the hormonal profile, and may promote a negative energy balance, contributing to body weight loss, but the influence on appetite control is still controversial. However, the amount of recent evidence showing that an acute session of moderate and intense exercise reduces energy intake in overweight and obese individuals has increased. Most of the advances in this field have been obtained with the use of animal models of obesity. Molecular analyses in the hypothalamic tissue have revealed that exercise improves anorexigenic signals in the hypothalamus of obese animals. Currently, the central anti-inflammatory response and myokines produced during muscle contraction are the main mechanisms explaining how physical exercise can recapitulate the hypothalamic anorexigenic signals in obese conditions. New studies and technologies are required to clarify in detail the impact of physical exercise on the control of food consumption.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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